

Beyond Pain: Using Unsupervised Machine Learning to Identify Phenotypic Clusters of Small Fiber Neuropathy

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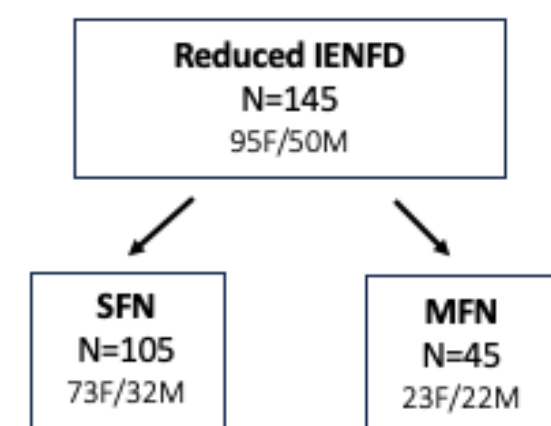
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Introduction

- Small fiber neuropathy (SFN) is characterized by dysfunction and loss of peripheral unmyelinated and thinly myelinated nerve fibers.
- The resulting phenotype includes varying combinations of somatosensory and dysautonomia symptoms, which can be profoundly disabling and lead to decreased quality of life.
- Treatment is aimed mainly at pain reduction, which may not target the underlying pathophysiology, is frequently ineffective.
- We hypothesize an impediment to the effective management of SFN may be the significant between-patient heterogeneity.

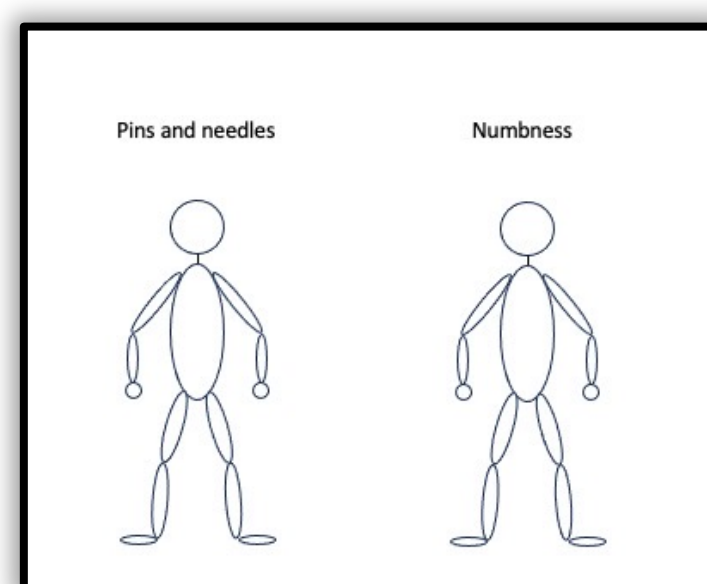
Materials and Methods

- 105 patients with skin-biopsy proven SFN and 45 with mixed fiber neuropathy (MFN) were recruited from Washington University Neuromuscular Clinic.



- Clinical data was collected via chart review.

- SFN symptoms: burning pain, numbness, pins and needles, myalgias, cramps, weakness, fatigue, and itch (Severity: 0 (absent) – 10 (maximal)).



- Dysautonomia symptoms: dry eyes, dry mouth, orthostatic hypotension, GI dysmotility, abnormal sweating, bladder incontinence, bowel incontinence (Frequency: 1 (never) - 4 (always)).

- To determine defining features of each cluster, comparison between the symptoms within each cluster was done using ANOVA and Kruskal-Wallis.

- Comparative analysis for demographic, clinical, skin biopsy, and laboratory finding data was done using chi-square for categorical variables and Mann-Whitney U test for continuous variables.

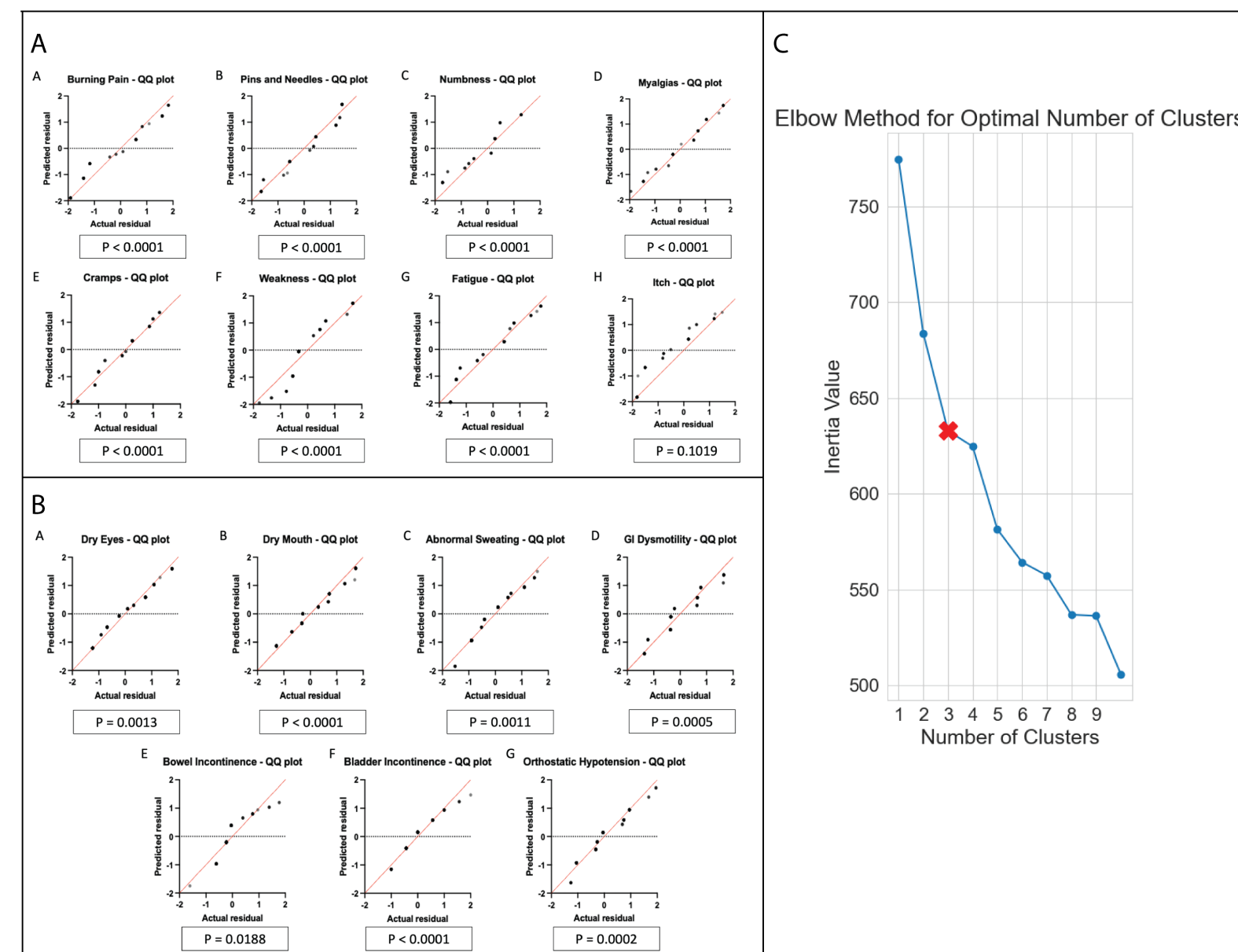


Figure 1: Elbow plot demonstrating the ideal number of clusters to be three. The point where the plot flexes, or 'elbows,' is the point of diminishing returns, whereby increasing cluster number offers no improved precision. QQ plots demonstrate the symptom severity data to be normally distributed, indicating the data is well-suited for ANOVA analysis.

SFN Exists as Three Distinct Phenotypes

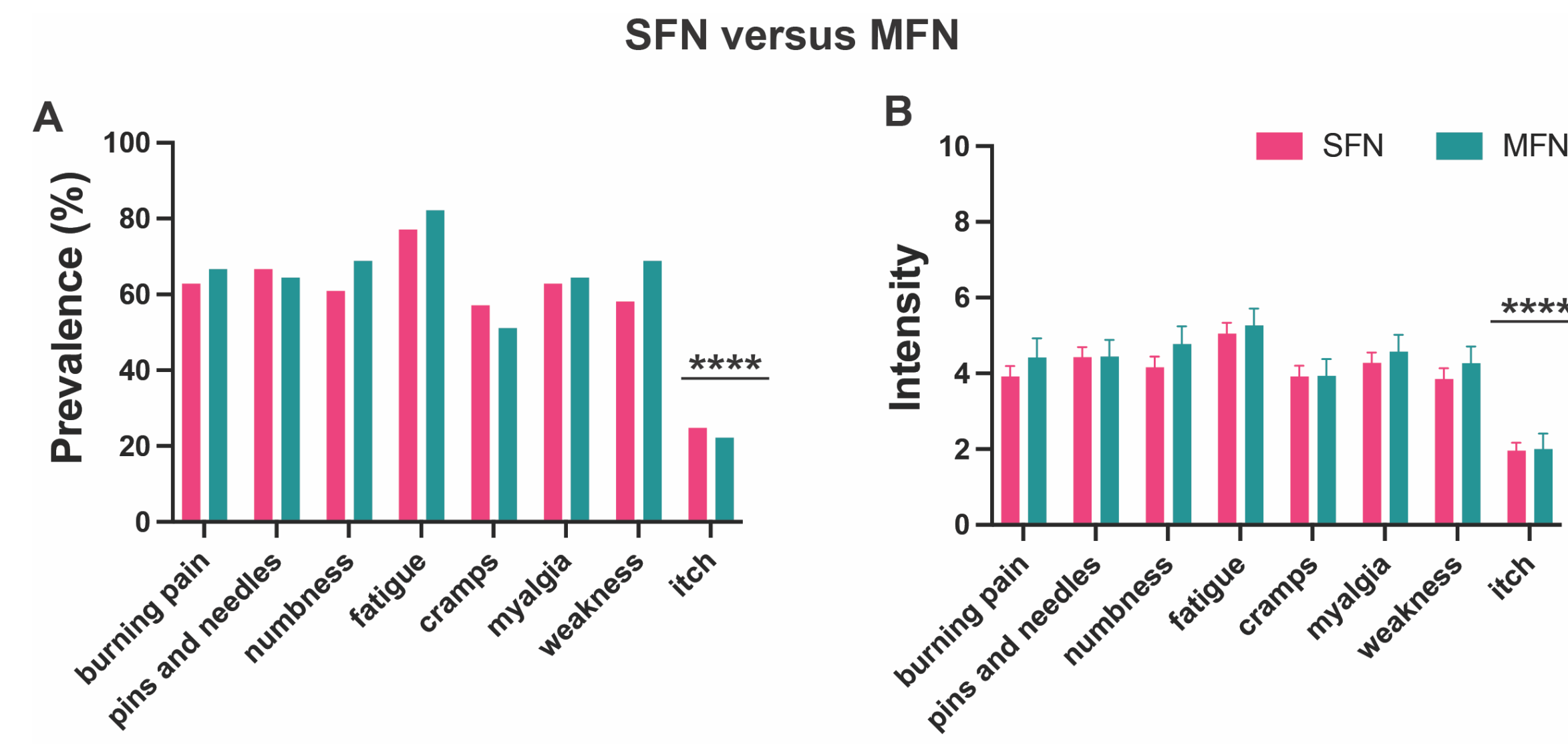


Figure 2: Symptom prevalence and severity of patients with small fiber neuropathy (SFN) and mixed fiber neuropathy (MFN). The prevalence (A) and severity (B) of symptoms was similar between patients with SFN and MFN. The symptom of 'itch' was reported by significantly fewer patients (A) and of significantly less intensity (B) by both patients with SFN ($p < 0.0001$, Kruskal-Wallis) and MFN ($p < 0.0001$).

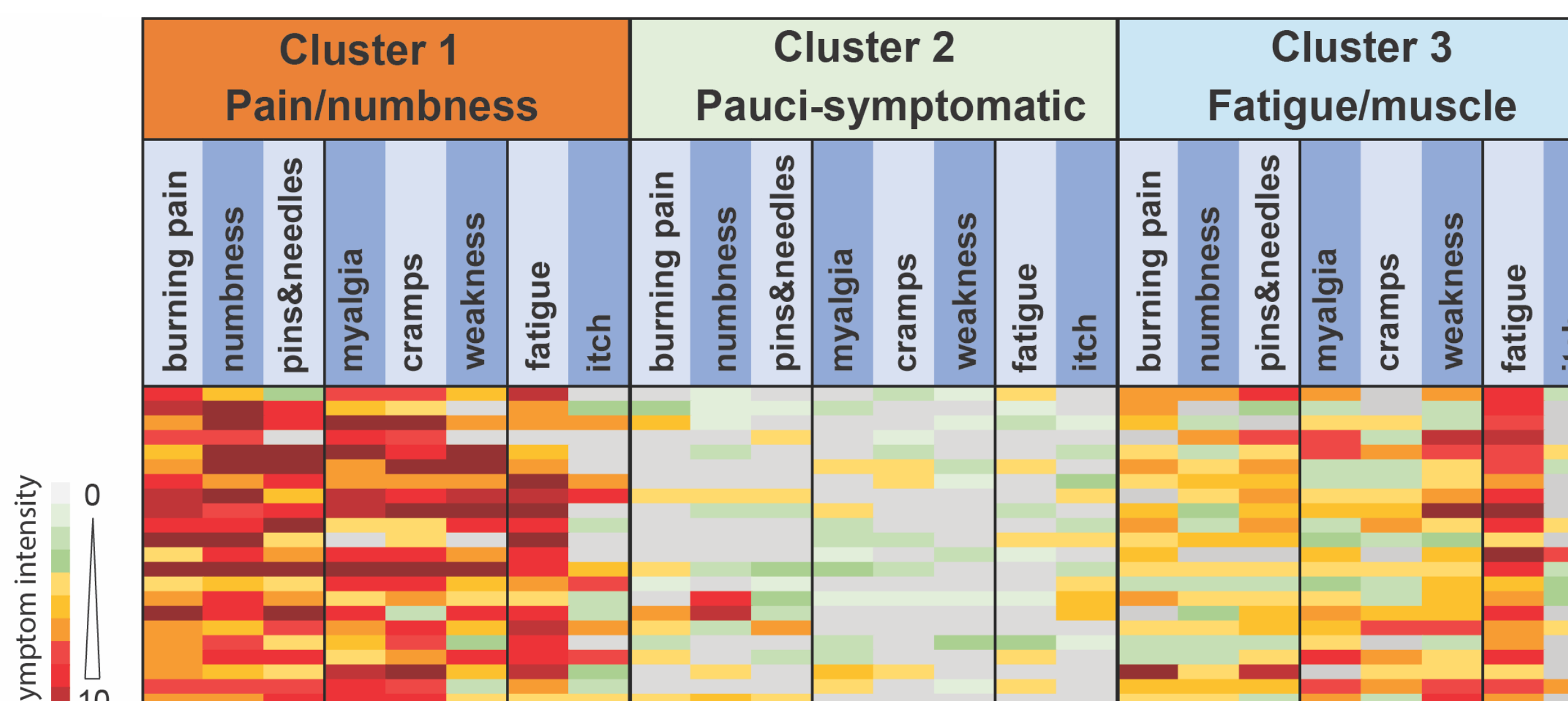


Figure 3: Heatmap of SFN symptom severities of twenty-two representative patients of each cluster. Each row in each cluster represents one individual patient. Note the high severity of most symptoms in cluster 1 (pain/numbness) and the high severity of fatigue in the cluster 3 (fatigue/muscle predominant), whereas patients in cluster 2 experienced mostly symptoms of low to moderate severities.

The SFN Phenotypes Differ in Symptom Intensity, Frequency, Concurrence, and Anatomical Localization

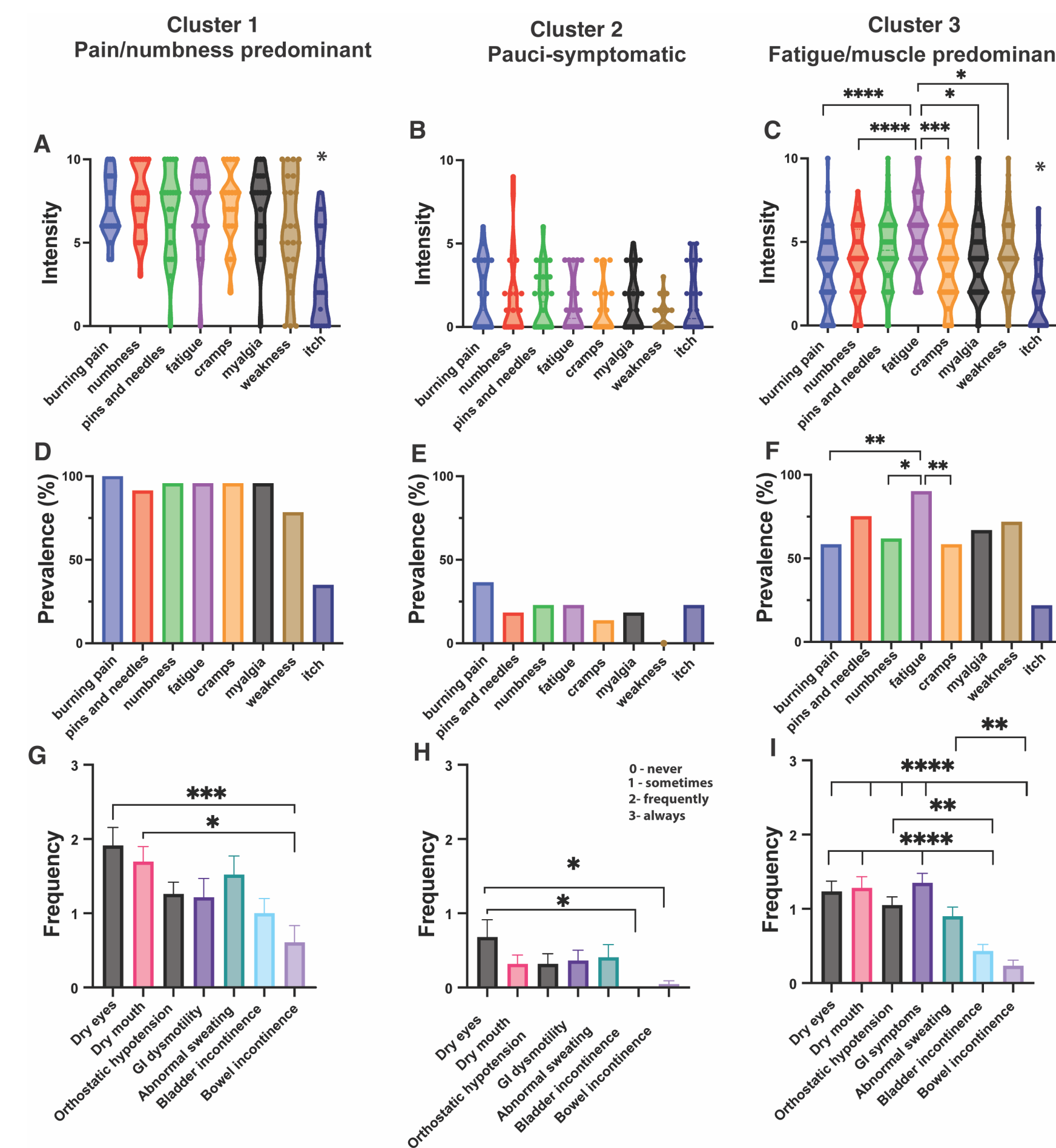


Figure 4: A-C: Comparison of symptom intensity in each cluster. A: Patients in cluster 1 experienced several symptoms at high intensity. B: Patients in cluster 2 experienced symptoms as generally less severe. C: Patients in cluster 3 had significantly more severe fatigue than burning pain ($p < 0.0001$, one-way ANOVA), numbness ($p < 0.0001$), cramps ($p = 0.0001$), myalgia ($p = 0.0195$), weakness ($p = 0.0294$) and itch ($p = 0.0011$). D-F: Prevalence of each symptom in the three clusters. The symptom of fatigue was reported by significantly more patients than burning pain ($p = 0.0004$, Kruskal-Wallis), numbness ($p = 0.0372$) and muscle cramps ($p = 0.0094$). G-I: Frequency of dysautonomia symptoms. G: Patients in cluster 1 had significantly less bowel incontinence than dry eyes ($p = 0.009$, one-way ANOVA) and dry mouth ($p = 0.0112$). H: Patients in cluster 2 had significantly less bowel ($p = 0.0269$, one-way ANOVA) and bladder incontinence ($p = 0.0133$) than dry eyes. I: Patients in cluster 3 experienced significantly less bowel and bladder incontinence than all other dysautonomia symptoms ($p < 0.0001$, one-way ANOVA). * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ and **** = $p < 0.0001$.

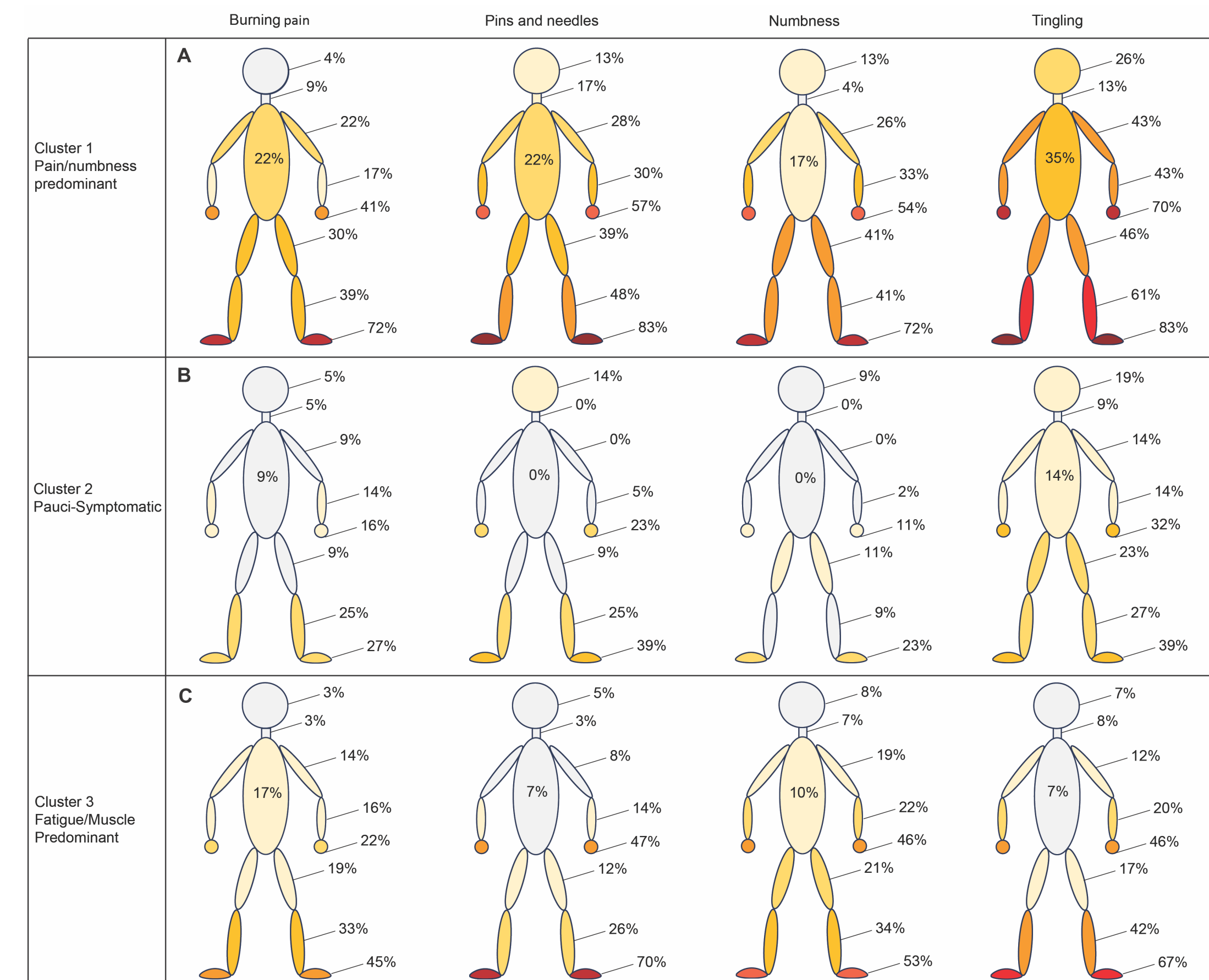


Figure 5: Localization of patient symptoms on a stick figure. Proximal symptoms were more commonly seen in the pain/numbness cluster, compared to the fatigue/muscle cluster and paucisymptomatic cluster. Interestingly, numbness was a rare symptom within the paucisymptomatic cluster, suggesting it is seen only in the more severe SFN phenotypes.

Conclusions

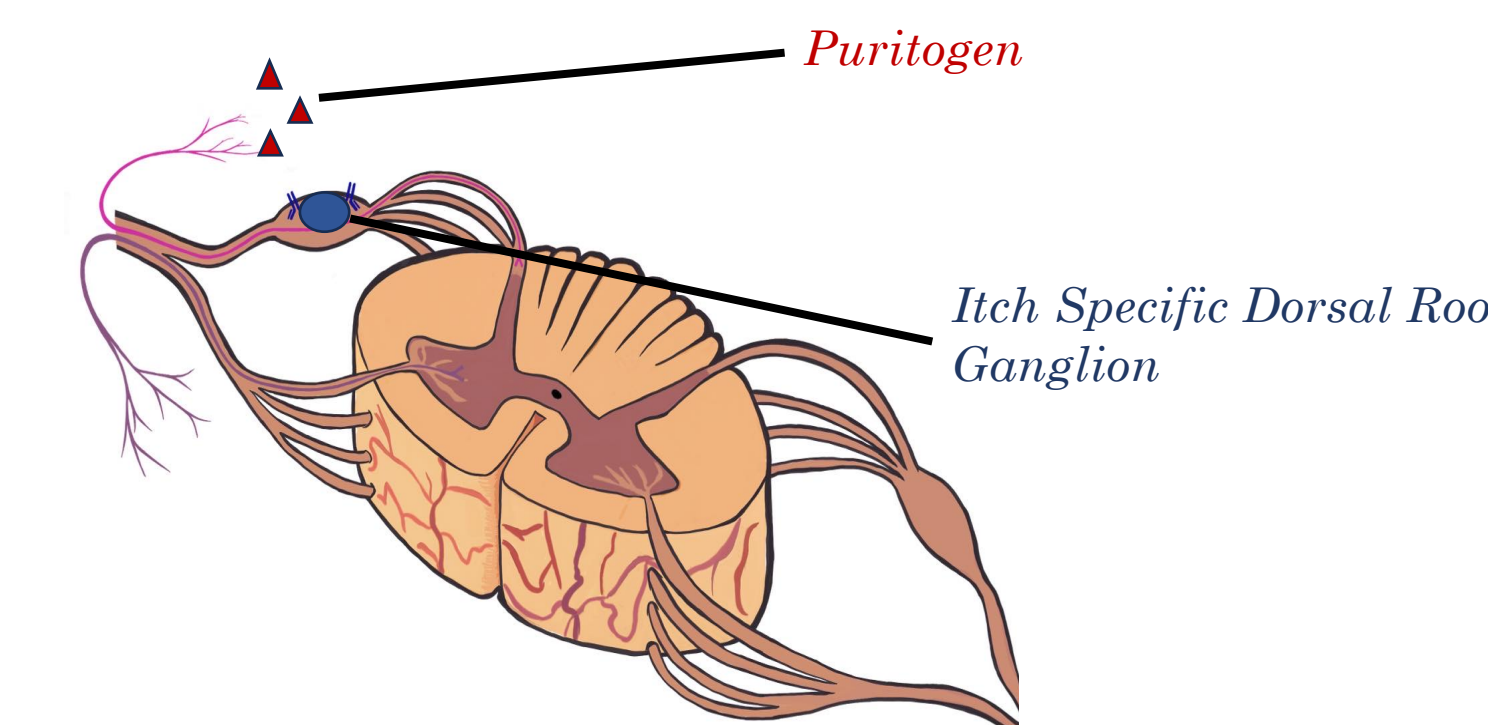
- SFN exists in three phenotypic clusters:
 - The first, 'pain/numbness predominant (n=23)', has many symptoms at high severity.
 - The second, 'paucisymptomatic' (n=22), has few symptoms, which when present, are low intensity.
 - The final, 'fatigue/muscle predominant' (n=60), displayed fatigue out of proportion to the other assessed SFN symptoms.
- Despite not including dysautonomia symptoms in the original phenotyping, the clusters displayed statistically significant variance by ANOVA for both 7/8 SFN symptoms and 6/7 dysautonomia symptoms.

Discussion

- This data-driven study introduces a new approach to subgrouping patients with SFN.
- Considering both neuropathic pain and pernicious symptoms beyond pain, we identified three clusters, which may be related to distinct pathophysiological mechanisms.
- Itch appears to occur independently of other SFN symptoms, suggesting a distinct pathophysiological mechanism.

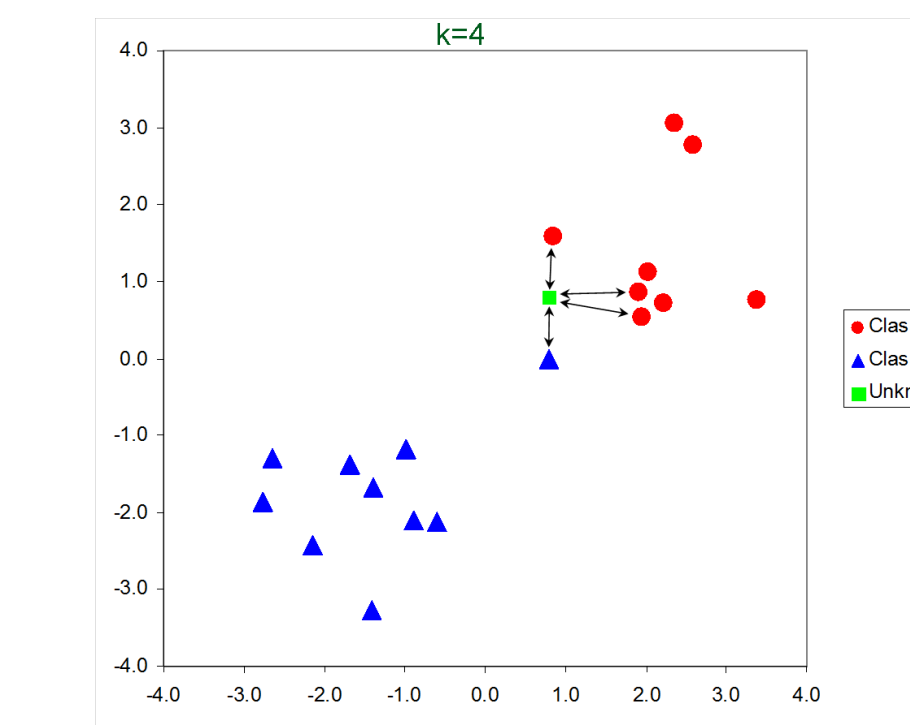
- Fatigue is a defining symptom of a large group of SFN patients.

- Although additional validation will be required, our findings represent a step towards stratified treatment approaches and, ultimately, personalized treatment.



Future Directions

- We will seek to identify biomarkers within the specific phenotypic clusters.
- We will seek to create and validate a forward predictive model, to allow for phenotyping of new patients.
- Assessing the efficacy of novel and established therapeutics with the SFN phenotypes.
- Explore applicability of novel therapeutic, such as SARM1 inhibitors, in the treatment of the SFN phenotypes.



(Peterson, LE. K-nearest neighbor. Scholarpedia. 2009; 1883)



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